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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,545	11/20/2001	Anthony J. Coyle	MPI1998-067CP2CN1A(M)	2144

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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,545	COYLE ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-39* is/are pending in the application.

4a) Of the above claim(s) *21,22,25 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20, 23, 24, 26, 28-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 20 – 39 are pending.

2. Applicant's election of Species 3A, directed to human ICOS (SEQ ID NO:12) in the reply filed on 09/07/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election with traverse of Species 4A, directed to a Th2 dependent inflammation response, in the reply filed on 09/07/2004 is acknowledged. The traversal is on the ground(s) that aspects of species as set forth are not necessarily distinct and may overlap and coincide in certain instances. Specifically, Applicant clarifies that activation of Species set forth as E (Th2-specific ligand interaction) is believed to result in activation of Species A (Th2 dependent inflammation response) as well as Species G (Th2 response which is inhibiting a Th1 immune response). In view of Applicant's argument, restriction of Species 4A - 4G has been withdrawn.

Applicant's election with traverse of Species 5A, directed to IL-4, in the reply filed on 09/07/2004 is acknowledged. The traversal is on the ground(s) that the search of the literature relating to ICOS mediated Th2 specific cytokine production would result in any of the cytokines named in the present requirement. This is not found persuasive

because the literature search for each individual cytokine would still be required in the interest of complete prosecution.

The requirement is still deemed proper and is therefore made FINAL.

Claims 21, 22, 25, and 27 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions.

Claims 20, 23 – 24, 26, and 28 – 39, as they read the elected species on human ICOS (SEQ ID NO:12), Th2-specific ligand interaction, Th2 dependent inflammation response, and Th2 response which is inhibiting a Th1 immune response; and IL-4 are under consideration in the instant application.

3. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The application USSN 09/413,136 upon which priority is claimed appears to provide adequate support under 35 U.S.C. 112 for subject matter claimed in the instant application.

However, applications USSN 09/258,670 and 09/168,229 upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for claims 20 – 39 of this application. Specifically, said applications do not appear to provide adequate support for the limitations of a method for modulating a Th2 response in a mammal by administering an ICOS polypeptide.

Consequently, the effective filing date of the instant claims is considered to be the filing date of USSN 09/413,136, i.e. 10/06/1999.

Should Applicant disagree with the Examiner's factual determination above, it is incumbent upon Applicant to provide a showing that specifically supports the instant claim limitations.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

In addition, Applicant should avoid the use of the word "novel" in the title, as patents are presumed to be novel and unobvious.

5. Applicant's IDS, filed 11/20/2001, is acknowledged, and has been considered. Reference #21 has been lined through as it is duplicative of reference #3.

6. The use of the trademarks, such as "PCR-select" and "PCRII" has been noted in this application at least on page 75. Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

In addition, Applicant is requested to review the application for embedded hyperlinks and/or other forms of browser-executable code and delete them. Embedded hyperlinks and/or other form of browser-executable code are impermissible in the text of the application as they represent an improper incorporation by reference. See MPEP § 608.01 and 608.01(p).

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is

requested in correcting any errors of which Applicant may become aware in the in the specification. For example, an apparent spelling error has been detected on page 16, line 12: "III-5."

7. It is noted that for examination purposes, the recitation of a "complement" sequence is interpreted to mean a complement over the full length of the reference sequence.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 20, 23 – 24, 26, and 28 –39 are rejected under 35 U.S.C. **112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 20, 23 – 24, 26, and 28 –39 are indefinite in the recitation of "a polypeptide having Th2-specific activity," because the metes and bounds of the phrase are unclear and ambiguous. Although the specification discloses on pages 15 – 16, bridging paragraph, several examples of "Th2-specific activity," the definition is not limiting to the examples, and moreover, the examples themselves do not clearly define the metes and bounds of what is meant by "Th2-specific activity." For instance, in Example 1: "modulating ... cellular proliferation, differentiation, and/or function," it is unclear which function is implied.

(B) The recitation of "hybridization under stringent conditions" in claims 20, 23 – 24, 26, and 28 –39 is indefinite in that it does not specify the metes and bounds of the hybridization conditions. Although the specification discloses on pages 23 - 24 general parameters for calculating such conditions, in the absence of a clear definition of the metes and bounds of this phrase it is unclear which conditions are actually claimed.

It is suggested that Applicant amend the claims to recite a specific set of hybridization and wash conditions to overcome this rejection.

(C) Claims 29, 34, and 35 are indefinite in the recitation of "Th2-specific ligand interaction," because it is unclear whether it is the ligand or its interaction partner that is Th2-specific. A skilled artisan would not be reasonably apprised of the metes and bounds of the claimed invention.

(D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 20, 23 – 24, 26, and 28 – 39 are rejected under 35 U.S.C. **112, first paragraph**, because the specification, while being enabling for a method for inhibiting a Th2 response in a mammal by administering a polypeptide comprising amino acid sequence SEQ ID NO:12, or its extracellular domain, ***does not reasonably provide enablement for:***

(A) a method for modulating or stimulating a Th2 response in a mammal;

(B) a method for inhibiting a Th2 response by administering a polypeptide having Th2-specific activity;

(C) a method for inhibiting a Th2 response by administering a polypeptide

1). comprising a fragment of SEQ ID NO:12;

2). having Th2-specific activity, encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to SEQ ID NO:11, or a complement thereof, or

3). having Th2-specific activity, encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:11, or a complement thereof under stringent conditions.

The specification does not provide a sufficient enabling description of the claimed invention.

The specification discloses on pages 81 – 87 some examples of inhibiting Th2 immune responses in vitro and in vivo by ICOS-Ig fusion protein. However, the instant claims encompass in their breadth methods for either inhibiting or stimulating Th2 response by administering a polypeptide comprising any fragment of the disclosed protein sequence, or any polypeptide having Th2-specific activity, which is encoded by a nucleic acid which either hybridizes to the disclosed sequence under stringent conditions, or is at least 95% identical to it.

(A) "Modulating/stimulating"

The specification, while being enabling for a method for inhibiting a Th2 response in a mammal, does not reasonably provide enablement for modulating or stimulating a Th2 response in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 20, 38, and 39 include recitations of "modulating" a Th2 response, and thus encompass in their breadth both inhibition and stimulation of the response.

The specification discloses on pages 81 – 87 working examples of inhibiting Th2 cell responses by ICOS-Ig fusion protein in vitro and in mouse models in vivo. However, insufficient guidance is provided for those skilled in the art as to the specific conditions which may stimulate a Th2 response.

In view of the lack of predictability of the art to which the invention pertains, and the lack of established protocols for effective stimulation of Th2 response by ICOS molecules, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for stimulating Th2 response.

(B) "Th2-specific activity"

Th2-specific activity, as defined on pages 15 – 16, bridging paragraph, includes in its breadth a wide range of direct and indirect activities, including stimulating and/or enhancing or inhibiting cellular proliferation, differentiation, and/or function, modulating Th2-specific immune response, inhibiting Th1 immune response, inducing and/or maintaining tolerance in both transplant and autoimmune diseases, binding Th2-specific ligand, or modulating Th2-specific cytokines such as IL-4, IL-5, IL-10, and IL-13.

The specification discloses on pages 81 – 87 working examples of inhibiting certain aspects of Th2 response, such as production of IL-4 and IL-5, IgE and IgG1 antigen-specific antibody production, and mucosal inflammation induced by antigen challenge. However, insufficient guidance is provided for those skilled in the art as to

the specific conditions which may affect the whole range of "activities" encompassed by the definition on pages 15 – 16. For example, Paul (Fundamental Immunology, 1999, Lippincott-Raven Publishers; pages 880 – 882) teaches that IL-10 and IL-4 expressions do not always correlate (page 882 first paragraph).

In view of the lack of predictability of the art to which the invention pertains, and the lack of established protocols for effective modulation of Th2-specific activities by ICOS molecules, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for modulating Th2-specific activities.

(C) Sequence issues:

1). "fragments"

The instant claim language encompasses fragments of the disclosed sequence of human ICOS, SEQ ID NO:12. However, the specification does not appear to have provided sufficient guidance as to which fragments of SEQ ID NO:12 would share the activity of inhibiting the production of IL-4 and IL-5, IgE and IgG1 antigen-specific antibody production, and mucosal inflammation induced by antigen challenge (with the exception of the fragment consisting of the extracellular domain of ICOS fused to an Ig fragment). Neither does the specification appear to have provided sufficient working examples of any other functional fragments. Thus it would require undue experimentation of the skilled artisan to determine which fragments of SEQ ID NO:12 would have the function of the disclosed molecule.

The term "comprising" in claims 20, 38, and 39 is open ended and extends the polypeptides to include additional non-disclosed sequences on either or both sides of the disclosed region. As the term "comprising" is applied to sequences other than full length ICOS or its disclosed extracellular domain, such as in "at least 15 contiguous amino acids," or "at least 50 contiguous amino acids," there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various polypeptides recited in the instant claims.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for the disclosed functional activities. Without detailed direction as to which amino acid sequences are essential to the function of the polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of amino acid sequences encompassed by the instant claims would share the ability of inhibiting the production of IL-4 and IL-5, IgE and IgG1 antigen-specific antibody production, and mucosal inflammation induced by antigen challenge, other than the disclosed ICOS molecule (SEQ ID NO:12) or its extracellular domain.

2). Percent Identity.

The claims recite a genus of polypeptides encoded by nucleic acid molecules comprising a sequence which is at least 95% identical to SEQ ID NO:12, but do not disclose which of the respective variants share any testable functional activity, a feature deemed essential to the instant invention. Applicant has disclosed two nucleic acid sequences and two corresponding protein sequences of human and mouse ICOS molecules, and thus has disclosed only two functional species. In the absence of some structural basis for the function that must be maintained by the members of the genus, the claimed invention is not described in such a way as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Attwood (Science, 2000, Vol. 290, pp. 471-473; in particular, second paragraph) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences." Similarly, Skolnick et al. (Trends in Biotech. 2000, Vol. 18, pp. 34-39; in particular, page 34) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Finally, even single amino acid differences can result in drastically altered functions between two costimulatory proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

In view of this unpredictability, the skilled artisan would not reasonably expect the claimed broad genus of polypeptides encompassed by the percent identity language to share the same function as the polypeptide of SEQ ID NO:12. The limitation of "having Th2-specific activity" is not seen as providing a requisite guidance because there is insufficient direction as to those essential sequences for the disclosed activities. Thus the teachings set forth in the specification provide no more than a plan or invitation for those skilled in the art to experiment practicing the claimed invention.

3). Hybridization.

Similarly, the fact that two nucleic acid sequences will hybridize under stringent conditions does not in and of itself require that the two corresponding polypeptides share any functional activity. It was well known in the art at the time the invention was made that hybridization could occur between two sequence based upon short stretches of 100% identity. Furthermore, the specification discloses on pages 23 – 24 that hybridization under stringent conditions allows to recover sequences which have as little as 60% identity to the target sequence. Thus a great deal of sequence variability with respect to the full-length nucleic acid is possible.

Thus hybridization language does not allow the skilled artisan to make and use the proteins encoded by the hybridizing nucleic acids commensurate in scope with the instant claims without undue experimentation, for reasons detailed above under "percent identity."

12. Claims 29 and 34 are rejected under 35 U.S.C. **112, first paragraph**, because the specification, while being enabling for a method for inhibiting a Th2 response which constitutes production of cytokines IL-4 and IL-5, does not reasonably provide enablement for inhibiting a Th2 response which constitutes production of

cytokines IL-10 or IL-13, or a broadly defined genus of "Th2 specific cytokines." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification discloses on page 84, first paragraph, that inhibition of ICOS leads to inhibition of production of IL-4 and IL-5. However, insufficient guidance is provided for those skilled in the art as to the specific conditions which may inhibit the production of IL-10 or IL-13, or other "Th2 specific cytokines." For example, Paul (Fundamental Immunology, 1999, Lippincott-Raven Publishers; pages 880 – 882) teaches that IL-10 and IL-4 expressions do not always correlate (page 882 first paragraph).

In view of the lack of predictability of the art to which the invention pertains, and the lack of established protocols for effective inhibition of IL-10 or IL-13 by ICOS molecules, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting production of said cytokines.

13. Claims 20, 23 – 24, 26, and 28 – 39 are rejected under 35 U.S.C. **112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The following ***written description*** rejection is set forth herein.

Applicant is in possession of a method for inhibiting a Th2 response in a mammal by administering a polypeptide comprising amino acid sequence SEQ ID NO:12, or its extracellular domain.

Applicant is not in possession of a method for inhibiting a Th2 response by administering a polypeptide:

(A) comprising a fragment of SEQ ID NO:12;

(B) having Th2-specific activity, encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to SEQ ID NO:11, or a complement thereof, or

(C) having Th2-specific activity, encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:11, or a complement thereof under stringent conditions.

The specification does not describe the claimed subject matter in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses on pages 81 – 87 some examples of inhibiting Th2 immune responses in vitro and in vivo by ICOS-Ig fusion protein. However, the instant claims encompass in their breadth methods for either inhibiting or stimulating Th2 response by administering a polypeptide comprising any fragment of the disclosed protein sequence, or any polypeptide having Th2-specific activity, which is encoded by a nucleic acid which either hybridizes to the disclosed sequence under stringent conditions, or is at least 95% identical to it.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Regarding the instant claim limitations, the specification does not appear to provide an adequate written description for the following reasons:

(A) "Fragments"

The instant claim language encompasses fragments of the disclosed sequence of human ICOS, SEQ ID NO:12. However, the specification does not appear to have provided sufficient written description as to which fragments of SEQ ID NO:12 would share the activity of inhibiting the production of IL-4 and IL-5, IgE and IgG1 antigen-specific antibody production, and mucosal inflammation induced by antigen challenge (with the exception of the fragment consisting of the extracellular domain of ICOS fused to an Ig fragment). Neither does the specification appear to have provided sufficient working examples of any other functional fragments. Thus it would require undue experimentation of the skilled artisan to determine which fragments of SEQ ID NO:12, other than the extracellular domain,+ would have the function of the disclosed molecule.

The term "comprising" in claims 20, 38, and 39 is open ended and extends the polypeptides to include additional non-disclosed sequences on either or both sides of the disclosed region. As the term "comprising" is applied to sequences other than full length ICOS or its disclosed extracellular domain, such as in "at least 15 contiguous amino acids," or "at least 50 contiguous amino acids," there does not appear to be sufficient written description in the specification as filed to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed methods.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient written description to direct a person of skill in the art to select particular sequences or sequence lengths as essential for the disclosed functional activities. Without detailed written description as to which amino acid sequences are essential to the function of the polypeptide, the specification does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the plethora of amino acid sequences encompassed by the instant claims which share the ability of inhibiting the production of IL-4 and IL-5, IgE and IgG1 antigen-specific antibody production, and mucosal inflammation induced by antigen challenge, other than the disclosed ICOS molecule (SEQ ID NO:12) or its extracellular domain.

(B) "Percent Identity."

The claims recite a genus of polypeptides encoded by nucleic acid molecules comprising a sequence which is at least 95% identical to SEQ ID NO:12, but do not disclose which of the respective variants share any testable functional activity, a feature deemed essential to the instant invention. Applicant has disclosed two nucleic acid sequences and two corresponding protein sequences of human and mouse ICOS molecules, and thus has disclosed only two functional species. In the absence of some structural basis for the function that must be maintained by the members of the genus, the claimed invention is not described in such a way as to convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Attwood (Science, 2000, Vol. 290, pp. 471-473; in particular, second paragraph) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences." Similarly, Skolnick et al. (Trends in Biotech. 2000, Vol. 18, pp. 34-39; in particular, page 34) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Finally, even single amino acid differences can result in drastically altered functions between two costimulatory proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus it is insufficient written description to convey to a skilled artisan whether any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

Given the absence of sufficient number of working examples of species that share the disclosed functional activities, the skilled artisan would not reasonably expect the claimed broad genus of polypeptides encompassed by the percent identity language to share the same function as the polypeptide of SEQ ID NO:12. The limitation of "having Th2-specific activity" is not seen as providing a requisite description because there is insufficient written description as to those essential sequences for the disclosed activities.

Thus the recitation of percent identity language does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(C) "Hybridization."

Similarly, the fact that two nucleic acid sequences will hybridize under stringent conditions does not in and of itself require that the two corresponding polypeptides share any functional activity. It was well known in the art at the time the invention was made that hybridization could occur between two sequence based upon short stretches of 100% identity. Furthermore, the specification discloses on pages 23 – 24 that hybridization under stringent conditions allows to recover sequences which have as little as 60% identity to the target sequence. Thus a great deal of sequence variability with respect to the full-length nucleic acid is possible.

Thus hybridization language does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the same reasons as detailed above under "percent identity."

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(e1) The invention was described in -

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published of a national application published under section 122(b) only if the international application designation the United States was published under Article 21(2)(a) of such treaty in the English language;

15. Claim 20, 23 – 24, 26, 28 – 33, and 36 are rejected under 35 U.S.C. **102(e)** as being anticipated by Tamatani et al. (Pat. Appl. Pub. US 2003/0083472; see entire document), as evidenced by Paul (Fundamental Immunology, 1999, Lippincott-Raven Publishers; pages 888 – 889) and by instant specification on pages 83 – 84.

Tamatani et al. teach a protein, JTT-1, which is 99% identical to the claimed hICOS protein (SEQ ID NO :12), including a region of 165 amino acids of 100% identity, as evidenced by the attached alignment (see entire document, in particular, pages 4 – 5 and SEQ ID NO:2).

Tamatani et al. teach that JTT-1 is expressed in thymocytes (i.e. T cells; Example 3 on page 22 and Figure 3) and functions in the regulation of lymphocyte activation (e.g. Example 13 on page 28). Tamatani et al. also teach that autoimmune diseases and allergic diseases can be treated by regulating the functions of the JTT-1 protein (paragraph 45). Tamatani et al. further teach that JTT-1 protein is involved in the transmission of costimulatory signal in regulation of T cells, similar to the CD28 and CTLA-4 molecules (Example 13, in particular, paragraphs 459 and 462).

Paul clarifies that CD28 and CTLA-4 molecules regulate (i.e. modulate) T helper cell responses, including both Th1 and Th2 responses (pages 888 – 889).

The instant application clarifies on pages 83 – 84, bridging paragraph, that ICOS-Ig fusion protein directly competes with membrane bound ICOS for binding with its putative ligand and hence blocks ICOS signaling.

Thus the above teachings of Tamatani et al., when viewed for all they teach, mean that ICOS-Ig fusion protein can be used for modulating Th2 cell response. Inherent in these teachings is a method for modulating a Th2 response in a mammal by administering ICOS-Ig.

Tamatani et al. further teach a polypeptide which is encoded by a DNA hybridizing with a DNA encoding JTT-1 (paragraph 57), a polypeptide comprising an amino acid sequence having 60% or more homology with an amino acid sequence of JTT-1 (paragraph 58), a polypeptide fragment comprising an extracellular region of JTT-1 (paragraph 67), a fusion protein of the extracellular domain of JTT-1 an a constant region of a human immunoglobulin heavy chain (paragraph 73), and a pharmaceutical composition of said protein and fusion protein, which is utilized for treating autoimmune and allergic diseases (paragraph 80) and inflammatory diseases (paragraph 27).

Claim 31 is included because, as acknowledged by Applicant in Response to restriction requirement, it is believed that Th2-specific ligand interaction would result in Th2 response that would be inhibiting Th1 immune response.

The reference teachings thus anticipate the claimed invention.

16. Claim 20, 23 – 24, 26, and 28 – 33, 35, 36, 38, and 39 are rejected under 35 U.S.C. **102(e)** as being anticipated by Kroczek (Pat. Appl. Pub. US 2002/0177191; see entire document).

Kroczek teaches a protein, 8F4, which is 97.7% identical to the claimed hICOS protein (SEQ ID NO :12), including a region of 130 amino acids of 100% identity, as

evidenced by the attached alignment (see entire document, in particular, paragraph 16 and SEQ ID NO:2), as evidenced by Paul (Fundamental Immunology, 1999, Lippincott-Raven Publishers; pages 888 – 889).

Kroczek teaches that 8F4 is expressed in T cells (Example 3 on page 5) and functions in costimulation of T cells (Example 5 on pages 5 – 6), and that this costimulation enhances the production of antibodies by B cells after interaction with 8F4-costimulated T cells (Example 6 on page 6). Kroczek also teaches that the 8F4 molecule can be used for therapy of disorders in which the immune system is involved, in particular for the treatment of asthmatic disorders (paragraph 1 and claim 32). Kroczek further teaches polypeptides having the biological activity of costimulation of T cells and having an amino acid sequence which shows at least 40% homology with the sequence of 8F4, or a biologically active fragments thereof (paragraph 15).

Paul clarifies that costimulation of T cells involves regulation of both Th1 and Th2 cells (page 888 – 889).

The reference teachings thus anticipate the claimed invention.

17. Conclusion: No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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October 28, 2004

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